ความสัมพันธ์ระหว่างการใช้ยากลุ่มยับยั้งโปรตอนปั๊มพ์และความเสี่ยงต่อโรคปอดอักเสบ: การศึกษาเชิงวิเคราะห์แบบย้อนหลัง
The Association between the Use of Proton Pump Inhibitors and the Risk of Pneumonia: A Case-Control Study

นิพนธ์ต้นฉบับ

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Original Article

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความสัมพันธ์ระหว่างยากลุ่มยับยั้งโปรตอนปั๊มพ์ (PPIs) กับการเกิดโรคปอดอักเสบในคนไข้ชาวไทย **วิธีการศึกษา:** การศึกษาเชิงวิเคราะห์แบบย้อนหลัง (case-control study) เปรียบเทียบระหว่างกลุ่มผู้ป่วยโรคปอดอักเสบที่สุ่มจากผู้ป่วยถูกวินิจฉัยตามรหัสโรคปอดอักเสบของ the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) และกลุ่มควบคุมเป็นผู้ป่วยรับบริการในวันและโรงพยาบาลเดียวกับกลุ่มศึกษา (อัตราส่วน 1:1) เก็บข้อมูลย้อนหลังจากฐานข้อมูลเวชระเบียนของผู้ป่วยในโรงพยาบาลพะเยาและโรงพยาบาลเชียงคำ จ.พะเยา ระหว่างมกราคม พ.ศ. 2555 ถึงธันวาคม พ.ศ. 2558 วิเคราะห์ความสัมพันธ์ระหว่างกลุ่มโดยใช้สถิติ Fisher's exact test และความสัมพันธ์แบบพหุตัวแปรโดยใช้พหุถดถอยลอจิสติกส์ โดยควบคุมตัวแปรเพศ อายุ กลุ่มโรคและกลุ่มยาของผู้ป่วย **ผลการศึกษา:** ผู้เข้าร่วมการศึกษาทั้งหมด 1,770 คน แบ่งเป็นกลุ่มผู้ป่วยโรคปอดอักเสบ 885 คน และกลุ่มควบคุม 885 คน ค่า adjusted odds ratio (OR_{Adj}) แสดงความสัมพันธ์ระหว่างยากลุ่ม PPIs และโรคปอดอักเสบเท่ากับ 1.47 (95% confidence interval [CI] = 1.08-2.01) โดยยา PPIs ในรูปแบบรับประทาน, (crude odds ratio (OR_{crude}) = 1.64, 95%CI = 1.29 – 2.09), รูปแบบผสมระหว่างรับประทานและฉีดเข้าหลอดเลือดดำ (OR_{crude} = 1.98, 95%CI = 1.08 – 3.63), การได้รับขนาด PPIs สะสมน้อยกว่า 50 defined daily dose (OR_{crude} = 1.87, 95% CI = 1.38 – 2.52) และ 50-100 defined daily dose (OR_{crude} = 1.99, 95% CI = 1.18 – 3.37) และระยะเวลาการใช้ยาน้อยกว่า 30 วัน (OR_{crude} = 2.87, 95%CI = 1.59 – 5.18) 30-90 วัน, (OR_{crude} = 1.68, 95% CI = 1.08 – 2.60) และมากกว่า 90 วัน (OR_{crude} = 1.46, 95% CI = 1.12 – 1.91) สัมพันธ์กับการเพิ่มโอกาสการเกิดโรคปอดอักเสบอย่างมีนัยสำคัญทางสถิติ **สรุป:** การใช้ยากลุ่ม PPIs สัมพันธ์กับการเกิดโรคปอดอักเสบ จึงควรตระหนักและวางแนวทางการใช้ยากลุ่ม PPIs ให้เหมาะสมสำหรับผู้ป่วย

คำสำคัญ: ยากลุ่มยับยั้งโปรตอนปั๊มพ์, โรคปอดอักเสบ, การศึกษาเชิงวิเคราะห์แบบย้อนหลัง

Abstract

Objective: To examine the association between the use of proton pump inhibitors (PPIs) and the risk of pneumonia in Thai patients. **Method:** We conducted a case-control study using medical records from Chiangkhum Hospital and Phayao Hospital between January 2012 and December 2015. We randomly selected cases who had a diagnostic code for any types of pneumonia according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) during the study period. Controls were identified through their date of hospital admission or hospital visit that matched with the diagnosis date of the cases (1:1). Fisher's exact test for univariate analyses and multiple logistic regression for multivariable analyses adjusted for gender, age, comorbid disease groups and co-medication groups were performed. **Results:** A total of 1,770 patients (855 cases and 855 controls) were identified. PPIs significantly increased the risk of pneumonia with an adjusted odds ratio (OR_{Adj}) of 1.47 (95% confidence interval [CI] = 1.08 - 2.01). Furthermore, oral PPIs, oral combined with parenteral PPIs, cumulative PPIs dose of < 50 defined daily dose (DDD) and of 50-100 DDD, and the use of PPIs of < 30 days, 30 – 90 days, and more than 90 days were independently associated with the increased risk of pneumonia with crude ORs of 1.64 (95% CI 1.29 – 2.09), 1.98 (95% CI 1.08 – 3.63), 1.87 (95% CI 1.38 - 2.52), 1.99 (95% CI 1.18 - 3.37), 2.87 (95% CI, 1.59 – 5.18), 1.68 (95% CI, 1.08 – 2.60), and 1.46 (95% CI, 1.12 – 1.91), respectively. **Conclusion:** The use of PPIs could be associated with an increased risk of pneumonia. Awareness among healthcare providers when prescribing PPIs should be raised.

Keywords: proton pump inhibitors, pneumonia, case-control study

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Introduction

Pneumonia has been one of major public health problems worldwide including Thailand. The World Health Organization (WHO) estimated 500,000 to 1.4 million deaths worldwide from pneumonia annually.[1,2] In the US, 1.3 millions of pneumonia cases with approximately 50,000 deaths were found in 2017.[3,4] In Thailand, based on the annual pneumonia incidence report of 2015 of Bureau of Epidemiology of Ministry of Public Health, there were 215,951 cases of pneumonia or

an incidence rate of 330.06 per 100,000 populations with a mortality rate of 0.74 per 100,000 populations. These incidence and mortality rates had been increasing during the past 10 years (2006 – 2015).[5] In terms of geographical difference, northern part of Thailand was the region with the most incidence rate in the past 10 years where the provinces with the highest rate found in provinces in the northern region including Mae Hong Son, Chiangrai and Phayao.[6]

Pneumonia is an acute respiratory disease caused by either bacteria, virus or fungi through inhalation or aspiration into the lung. Symptoms of pneumonia include fever or chill, difficulty breathing, cough, pus-like sputum, rapid breathing, chest pain with cough or inhalation. The diagnosis is confirmed by culture laboratory investigation.[7] Five types of pneumonia include community-acquired (CAP), hospital-acquired (HAP), ventilator-associated (VAP), aspiration (AP), and healthcare-associated pneumonia (HCAP).[8]

Proton pump inhibitors (PPIs) exert their acid secretory reduction by inhibiting hydrogen–potassium adenosine triphosphatase enzyme at the parietal cells of the stomach.[9] In 2011, there were more than 60 million prescriptions for PPIs in the US[10] which were worth 10 – 15 thousand million US dollars.[11] In Thailand, the prescriptions for PPIs were worth as high as 632 million bahts and were on the top-five of medications prescribed for outpatients under the Civil Servant Medical Benefit Scheme (CSMBS) in the fiscal year of 2009.[12] PPIs licensed with Thailand Food and Drug Administration include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole[13] with only omeprazole and pantoprazole included in the National List of Essential Drugs.[14]

PPIs are indicated for various disorders in the upper gastrointestinal tract including esophagitis, peptic ulcer, gastro-esophageal reflux disease (GERD), and dyspepsia.[9,12,15] Despite their medical benefits and popularity, PPIs could cause adverse events from mild to severe ones. The life-threatening adverse effects of PPIs consist of pneumonia, bone fracture, and gastrointestinal infection.[16] Pneumonia associated with PPIs has been found to increase and receive more clinical attention. Four of the five types of pneumonia associated with PPIs were CAP, HAP, AP, and VAP.[17-20]

Previous international studies found that PPIs increased the risk of pneumonia by 1.27 folds when compared with no PPI use.[18] The risk of CAP was increased by 1.73 folds among PPI users.[21] Factors associating with pneumonia were age, chronic disease, and duration and dose of PPIs.[21-27] The elderly were more likely to have PPI-related CAP.[23] A duration of PPI use of less than 30 days was associated with an increased risk of pneumonia.[21] The highest incidence of pneumonia was found within the first seven days of PPI dosing. The risk of pneumonia was associated with PPI's defined daily dose (DDD); the more the DDD, the higher the risk of pneumonia.[22] A study found that PPI use was associated with 1.3 folds of risk of pneumonia in the hospital when compared with PPI nonusers.[28] However, another study found no association.[29] The risk of aspiration pneumonia was also 1.4 times among PPI users when compared with nonusers.[28] Furthermore, 88.5% of patients with VAP were found to have a history of PPI use.[30]

Patients with stroke[24,25], chronic kidney disease[26] and chronic obstructive pulmonary disease (COPD)[27] are more likely to have pneumonia. Patients with these illnesses could have had gastrointestinal abnormalities regarding acid hypersecretion which needs PPIs for treatment. Pneumonia as a complication could be a result and the risk of death among these patients could be increased.[24-27]

There has been a concern about the increase in pneumonia incidence and PPI prescriptions worldwide including Thailand with the association between the use of PPIs and the risk of pneumonia both in general patients and patients with specific illnesses including stroke and chronic kidney disease. With differences in the patient demographic characteristics, the relationship between the use of PPI use and the risk of pneumonia in Thailand could be different from other countries and deserved to be determined. In this present study, we aimed to examine the association between the use of PPIs and pneumonia in Phayao province which is one of the 10 provinces with the highest pneumonia incidence in Thailand. We also aimed to determine the association between route of administration, duration of use, and cumulative dose of PPIs and the risk of pneumonia.

Methods

In this case-control study, data of patients receiving care from January 1, 2012 to December 31, 2015 at Phayao Hospital and Chiangkhum Hospital in Phayao province were obtained from medical records. The study was approved by the Ethics Committee for Human Study of University of Phayao (approval number: 2/047/59; approval date: June 1, 2016), of

Phayao Hospital (approval number: HE-59-02-0055; approval date: September 15, 2016) and of Chiangkhum Hospital (approval number: 04/2559; approval date: September 1, 2016).

Population and sample

Study population included patients aged 20 years or older receiving either out- or in-patient care at Phayao Hospital or Chiangmai Hospital. Cases were those diagnosed with pneumonia based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes of J13-J18 and J69. Controls were patients not diagnosed with pneumonia.

Patients with the following illnesses or conditions were excluded: acquired immune deficiency syndrome, infection with human immunodeficiency virus, systemic lupus erythematosus (SLE), neutropenia, or transplantation of organ or bone marrow. Patients with these illnesses or conditions were immunocompromised which could have an increased risk of pneumonia.

Sampling method

Two steps of sampling were conducted. Cases were selected by simple random sampling on all pneumonia cases during the study period. Codes on patients were created by an assigned individual not associated with the sampling process. Controls were selected by randomly selecting a patient that was matched with a case on the case's diagnosis date of pneumonia and on the hospital with a matching ratio of case to control of 1 to 1. The matching on diagnosis date and hospital between cases and controls could reduce confounding related to the two factors on medication prescription pattern over time and place. Specifically, hospital drug list could be revised every time, availability of medication products could be dependent on the market, and the shortage of specialists could affect prescribing PPIs.

Sample size was estimated based on the unmatched case-control study design using the equation of Kelsey and colleagues.[31] With an error of 5% and a confidence level of 95%, a sample size of 576 patients per group (or a total of 1,152 patients) was required. To compensate for attrition rate, a 20% compensation rate was applied and resulted in a sample size of 692 patients per group (or a total of 1,384 patients) was recruited.

Data of PPI use in cases and controls were extracted from medical records. The use of PPI was started at the diagnosis date of pneumonia (index date) as indicated by the ICD-10 codes of pneumonia (J13 - J18 and J69) from the hospital database system called HosXP™. The extent of PPI use was the accumulation of amount of PPI prescribed within six months before the index date. It has been found that pneumonia was significantly found within the six months of PPI use,[18,21] but such significant association was not found after the six months period.[19,21]

The exposure of PPI use was referred to the cumulative dose which was measured as numbers of defined daily dose (DDD). DDD was the average maintenance dose per day for a drug used for its main indication in adults as indicated by the WHO. For example, DDD values for omeprazole were 20 mg given orally and 20 mg given parenterally.[32] The exposure of PPI during six months before the index date was calculated as cumulative dose for each patient. If more than one administration methods of a given PPI and/or more than one kind of PPI was used for a given patient, DDD doses of each administration method and each kind of PPI were summed up.

In terms of potential confounding factors to be concomitantly tested with the use of PPI, there were selected based on literature review.

Study instrument

Data collection form and HosXP™ medical records database of the two study hospitals were used in this study. The information recorded on the data collection form included gender, age, dose of PPI, duration of PPI use, administration route of PPI, history of chronic illness, medication history other than PPIs, bed-ridden status, history of smoking and alcohol drinking.

Data analysis

Descriptive statistics was used to present demographic and clinical status characteristics including frequency with percentage. Differences of demographic and clinical status characteristics between cases and controls were tested using Chi-square test or Fisher's exact test, as appropriate. The risk of pneumonia in relation to PPI use was examined using logistic regression. Risk of pneumonia was presented as odds ratio (OR) with 95% confidence interval (95% CI). Specifically, for the association the risk of pneumonia and PPI use alone, binary logistic regression was used and the risk was presented

as crude OR. Multiple logistic regression was used to examine such association adjusted for other potential confounders and the risk was presented as adjusted OR. Statistical analysis was set a type I error of 4% (or P-value < 0.05). All statistical analyses were performed using STATA version 12 software.

Results

Of the 1,770 patients eligible for study inclusion, there were 885 cases and 885 controls. Significant differences between cases and controls were gander, age, and smoking (Table 1). For medications, cases and controls were in different proportions with autonomic nervous system drugs, analgesic/anti-inflammatory drugs, gastrointestinal drugs, endocrine system drugs, antibiotic/cytotoxic drugs, ear, eye, nose and throat drugs, and vitamins, minerals, and supplements. In terms of co-morbidities, cases and controls were different in kidney failure, respiratory disorder, urinary tract diseases and hematological disorders (Table 1).

Table 1 Characteristics of the participants (N = 1,770).

Characteristics	N (%)		*P*-value
	Cases (n = 885)	Controls (n = 885)	
Gender			
Female	416 (47.01)	513 (57.97)	0.001
Male	469 (52.99)	372 (42.03)	
Age (year)			
< 40	47 (5.31)	170 (19.21)	
40 - 60	200 (22.60)	420 (47.46)	< 0.001
> 60	638 (72.09)	295 (33.33)	
Medications			
Autonomic nervous drugs	385 (43.50)	231 (26.10)	< 0.001
Central nervous drugs	289 (32.66)	280 (31.64)	0.684
Cardiovascular drugs	296 (33.45)	287 (32.43)	0.686
Analgesic/anti-inflammatory drugs	449 (50.73)	398 (44.97)	0.015
Endocrine system drugs	212 (23.95)	123 (13.90)	< 0.001
Antibiotics/cytotoxic drugs	234 (26.44)	163 (18.42)	< 0.001
Gastrointestinal drugs	233 (26.33)	163 (18.42)	< 0.001
Ear, eye, nose and throat drugs	256 (28.93)	78 (8.81)	< 0.001
Vitamins, minerals, and supplements	346 (39.10)	248 (28.02)	< 0.001
Others	12 (1.36)	14 (1.58)	0.844
Comorbidities			
Cardiovascular diseases	599 (67.68)	591 (66.78)	0.723
Kidney failure	124 (14.01)	27 (3.05)	< 0.001
Endocrine disorders	84 (9.49)	99 (11.19)	0.274
Respiratory illnesses	193 (21.81)	42 (4.75)	< 0.001
Urinary tract diseases	25 (2.82)	12 (1.36)	0.045
Musculoskeletal disorders	60 (6.78)	64 (7.23)	0.780
Cancer	31 (3.50)	17 (1.92)	0.056
Nervous system and brain disorders	45 (5.08)	54 (6.10)	0.408
Psychiatric disorders	41 (4.63)	44 (4.97)	0.824
Dermatological diseases	6 (0.68)	6 (0.68)	1.000
Hematological disorders	43 (4.86)	14 (1.58)	< 0.001
Gastrointestinal disorders	72 (8.14)	70 (7.91)	0.930
Ear, eye, nose and throat diseases	26 (2.94)	20 (2.26)	0.455
Infectious diseases	45 (5.08)	35 (3.95)	0.303
Bed-ridden patients	5 (0.56)	4 (0.45)	1.000
Smoking			
Yes	111 (17.16)	47 (7.67)	< 0.001
No	536 (82.84)	566 (92.33)	
Alcohol drinking			
Yes	92 (14.92)	86 (13.98)	0.936
No	552 (85.71)	529 (86.02)	

PPIs prescribed during study period (2012 – 2015) in the two study hospitals were as follows. In Phayao Hospital, three oral products (omeprazole, rabeprazole and esomeprazole) and two parenteral products (omeprazole and pantoprazole) were used. On the other hand, only omeprazole both with oral and parenteral products were used in Chiangkhum Hospital.

It was found that the use of PPI was found in 27.12% of cases and 18.42% of controls (Table 2). The use of PPI was associated with a statistically significant increased risk of pneumonia with a crude OR of 1.65 (95% CI = 1.31 - 2.08). The use of PPIs was still significantly associated the risk of pneumonia with an adjusted OR of 1.47 (95% CI = 1.08 - 2.01) when potential confounders were taken into accounted altogether. These potential confounders included gender, age, smoking, the use of autonomic nervous system drugs, analgesic/anti-inflammatory drugs, endocrine system drugs, antibiotic/cytotoxic drugs, ear, eye, nose and throat drugs, and vitamins, minerals, and supplements, and co-morbidities of kidney failure, respiratory disorder, cancer and hematological disorders (Table 2).

Among all potential confounders, it was found that there were confounders that were significantly associated with the increase in risk of pneumonia and those with the decrease in pneumonia risk. Factors that were significantly associated with the increased risk of pneumonia included age of 60 years old or older (OR_{Adj} = 3.92, 95% CI = 2.53 – 6.06), smoking (OR_{Adj} = 2.40, 95% CI = 1.58 – 3.65), kidney failure (OR_{Adj} = 5.15, 95% CI = 3.01 – 8.79), hematological disorder (OR_{Adj} = 2.68, 95% CI = 1.19 - 20.98), respiratory disorder (OR_{Adj} = 2.39, 95% CI = 1.51 – 3.81), and medications for ear, eye, nose, throat disorders (OR_{Adj} = 2.89, 95% CI = 1.99 – 4.20). On the other hand, factor that was significantly associated with the decreased risk of pneumonia was analgesic/anti-inflammatory drugs (OR_{Adj} = 0.62, 95% CI = 0.45 – 0.85). All other factors including gender, age of less than 60 years old, autonomic nervous drugs, endocrine drugs, antibiotic/cytotoxic drugs, vitamins, minerals, and supplements, and cancers were not significantly associated with the risk of pneumonia.

In terms of specific contribution of PPIs on the risk of pneumonia, oral route (OR_{crude} = 1.64, 95% CI = 1.29 – 2.09) and oral combined with parenteral route (OR_{crude} = 1.98, 95% CI = 1.08 – 3.63) were significantly associated with the increased risk of pneumonia when compared with no PPI use; while parenteral route was not. For duration of PPI use, all use duration categories (i.e., < 30 days, 30 – 90 days, and >

90 days) were significantly associated with the increased pneumonia risk compared with no PPI use [(OR_{crude} = 2.87, 95% CI = 1.59 – 5.18), (OR_{crude} = 1.68, 95% CI = 1.08 – 2.60) and (OR_{crude} = 1.46, 95% CI = 1.12 – 1.91), respectively]. For the cumulative dose of PPI, the dose of less than 50 DDD (OR_{crude} = 1.87, 95% CI = 1.38 - 2.52) and 50 – 100 DDD (OR_{crude} = 1.99, 95% CI = 1.18 - 3.37) were significantly associated with the increased risk of pneumonia when compared with no PPI use; while the dose of more than 100 DDD was not.

Table 2 The association of the use of PPIs and other factors with the risk of pneumonia (N = 1,770).

Variables	N (%)		Crude OR (95% CI)	Adjusted OR# (95% CI)
	Cases (n = 885)	Controls (n = 885)		
Use of PPIs				
Yes	240 (27.12)	163 (18.42)	1.65 (1.31 - 2.08)	1.47 (1.08 - 2.01)
No	645 (72.88)	722 (81.58)	Ref	Ref
Gender				
Female	416 (47.01)	513 (57.97)	X	0.79 (0.61 – 1.03)
Male	469 (52.99)	372 (42.03)	X	Ref
Age (years)				
> 60	638 (72.09)	295 (33.33)	X	3.92 (2.53 – 6.06)
40 – 60	200 (22.60)	420 (47.46)	X	1.23 (0.78 – 1.93)
< 40	47 (5.31)	170 (19.21)	X	Ref
Smoking				
Yes	111 (17.16)	47 (7.67)	X	2.40 (1.58 – 3.65)
No	536 (82.84)	566 (92.33)	X	Ref
The use of autonomic nervous system drugs				
Yes	385 (43.50)	231 (26.10)	X	1.13 (0.83 – 1.54)
No	500 (56.50)	654 (73.90)	X	Ref
The use of analgesic/anti-inflammatory drugs				
Yes	450 (50.85)	398 (44.97)	X	0.62 (0.45 – 0.85)
No	435 (49.15)	487 (55.03)	X	Ref
The use of endocrine system drugs				
Yes	212 (23.95)	123 (13.90)	X	0.93 (0.66 – 1.30)
No	673 (76.05)	762 (86.10)	X	Ref
The use of antibiotic/cytotoxic drugs				
Yes	234 (26.44)	163 (18.42)	X	1.25 (0.90 – 1.74)
No	651 (73.56)	722 (81.58)	X	Ref
The use of ear, eye, nose and throat drugs				
Yes	256 (28.93)	78 (8.81)	X	2.89 (1.99 – 4.20)
No	629 (71.07)	807 (91.19)	X	Ref
The use of vitamins, minerals, and supplements				
Yes	346 (39.10)	248 (28.02)	X	0.88 (0.65 – 1.19)
No	539 (60.90)	637 (71.98)	X	Ref
Comorbidities of kidney failure				
Yes	124 (14.01)	27 (3.05)	X	5.15 (3.01 – 8.79)
No	761 (85.99)	858 (96.95)	X	Ref
Comorbidities of respiratory disorders				
Yes	193 (21.81)	42 (4.75)	X	2.39 (1.51 – 3.81)
No	692 (78.19)	843 (95.25)	X	Ref
Comorbidities of cancer				
Yes	31 (3.50)	17 (1.92)	X	1.24 (0.58 – 2.65)
No	854 (96.50)	868 (98.08)	X	Ref
Comorbidities of hematological disorders				
Yes	43 (4.86)	14 (1.58)	X	2.68 (1.25 – 5.75)
No	842 (95.14)	871 (98.42)	X	Ref

Note: OR = odds ratio; 95% CI = 95% confidence interval.

Adjusted for potential confounders including potential confounders including gender, age, smoking, the use of autonomic nervous system drugs, analgesic/anti-inflammatory drugs, endocrine system drugs, antibiotic/cytotoxic drugs, ear, eye, nose and throat drugs, and vitamins, minerals, and supplements, and co-morbidities of kidney failure, respiratory disorders, cancer and hematological disorders.

Table 3 The association between the risk of pneumonia and PPI's route of administration, use duration, and cumulative dose (N = 1,770).

Variables	N (%)		Crude odds ratio (95% CI)
	Cases (n = 885)	Controls (n = 885)	
Administration route of PPIs			
Oral	205 (23.16)	140 (15.82)	1.64 (1.29 – 2.09)
Parenteral	6 (0.68)	5 (0.56)	1.35 (0.41 – 4.44)
Oral with parenteral	30 (3.39)	17 (1.92)	1.98 (1.08 – 3.63)
No PPI use			Ref.
Duration of PPIs use (Day)			
> 90	145 (16.38)	111 (12.54)	1.46 (1.12 – 1.91)
30 - 90	54 (6.10)	36 (4.07)	1.68 (1.08 – 2.60)
< 30	41 (4.63)	16 (1.81)	2.87 (1.59 – 5.18)
0 (no PPI use)			Ref.
Cumulative dose of PPIs (Defined daily dose; DDD)*			
> 100 DDD	67 (7.57)	61 (6.89)	1.23 (0.86 – 1.77)
50 – 100 DDD	41 (4.63)	23 (2.60)	1.99 (1.18 – 3.37)
< 50 DDD	132 (14.92)	79 (8.93)	1.87 (1.38 – 2.52)
0 (no PPI use)			Ref.

Note: 95% CI = 95% confidence interval.

Defined daily dose (DDD) was the average maintenance dose per day for a drug used for its main indication in adults as indicated by the WHO.

Discussions and Conclusion

The use of proton pump inhibitors (PPIs) was assocaied with the risk of pneumonia in patients from Phayao province, Thailand. The risk of pneumonia was significantly increased with administration of oral route, administration of oral combined with parenteral route, cumulative dose of less than 50 DDD and of 50 – 100 DDD, and duration of PPI use of less than 30 days, 30 – 90 days, and more than 90 days when compared with no PPI use.

Other risk factors significantly increased the risk of pneumonia included age of more than 60 years or older, smoking, kidney failure, hematological disorders, resptiratory disorders, and drugs for ear, eye, nose and throat illnesses; while factors significantly decreased pneumonia risk was analgesic/anti-inflammatory drugs. These risk factors should prompt healthcare providers to be vigilant about the risk of pneumonia among patients with these potential risk factors using PPIs. This care could be considered a rational drug use.

The use of PPIs was significantly associated with pneumonia with an increased risk of 1.47 folds compared with not using (adjusted OR = 1.47, 95% CI = 1.08 - 2.01). Our finding was consistent with the result of a meta-analysis where a significant increasd risk of pneumonia with PPI use (OR = 1.27, 95% CI = 1.11 – 1.46) when compared with no PPI use.[18] Our finding was also consistent with previous studies where the effect of PPIs was consistent across all types of pneumonia, either CAP or HAP.[18,21,28,30,33]

Pneumonia could be caused by PPIs by four different pathophysiology pathways as follows. First, the inhibition of acid secretion by inhibiting hydrogen potassium adenosine triphosphatase enzyme (H^+/K^+-ATPase) in the parietal cells of the stomach. An increased gastric pH caused by PPIs could allow more bacterial growth and number in upper gastrointestinal tract. As a result, more bacteria could pass to the lung via aspiration.[18,34] Second, the acid secretion inhibition through H^+/K^+-ATPase enzyme in the respiratory tract could also cause an increase in pH, a decrease in mucus secretion and ultimately an increase in bacterial growth in respiratory tract.[18,34] Third, the increased pressure on the lower gastric sphincter could force gastric content to move up to esophagus and be more prone to aspiration of the gastric content and bacteria into the lung.[34,35] Last, the use of PPI might inhibit the functions of certain white blood cells such as neutrophils, natural killer cells and T-cells. Such inhibition could damage the bacterial inhibition effects of these cells, hence the increased bacteria cell numbers and the increased risk of lung infection.[18,36]

Our study was the the first to find the association of PPI use and pneumonia regarding administration route. The risk of pneumonia was increased by oral route (crude OR = 1.64, 95% CI = 1.29 – 2.09) and the oral route combined with parenteral route (crude OR = 1.98, 95% CI = 1.08 – 3.63), when compared with no PPI use. The non-significant finding of parenteral route could be attributable to a relatively small number of patients using PPIs with only 6 patients in cases and 5 patients in controls. Most patients with PPI use took PPIs by oral route, followed by oral route combined with parenteral route, and parenteral route, respectively.

The trend of PPI use and prescription could be influenced by at least three factors. Since omeprazole is a category A PPI in the National List of Essential Drugs of Thailand, it is thus more compeling for prescription before other PPIs.[14] In addition, oral route of PPI is recommended by the standard guidelines for upper gastrointestinal disorder concering abnormal acid secretion such as dyspepsia, peptic ulcer, and GERD.[37-41] As a reslt, oral PPIs are the most used drugs, hence the largest number of patients taking the drugs orally.

The combined use of oral and parenteral PPIs (crude OR = 1.98, 95% CI = 1.08 – 3.63) seemed to cause pneumonia with a stronger association than that of oral route (crude OR = 1.64, 95% CI = 1.29 – 2.09). This could be attributable to a larger portion of drug into the systemic circulation through parenteral administration when compared with oral route which have bioavailability of 40 – 80%.[15] Thus parenteral route of PPI could possibly cause more pathological abnormality in the lung than oral PPIs. Ultimately, the risk of pneumonia in those taking parenteral and oral PPIs was greater than those taking only oral PPIs.

Duration of PPI use was significantly assocaied with the risk of pneumonia at all lengths (i.e., less than 30 days, 30 – 90 days, and more than 90 days) compared with no use of PPI. The interesting finding was that the longer the use, the lower the risk of pneumonia. Specificlly, crude ORs decreased from 2.87, to 1.68 and 1.46 for durations of less than 30 days, 30 – 90 days, and more than 90 days, respectively. This decling risk of pneumonia over time was consistent with the previous meta-analysis study where ORs were 3.95 (95% CI = 2.86 – 5.45), followed by 1.61 (95% CI = 1.46 – 1.78), and 1.36 (95% CI = 1.05 – 1.78) for durations of within 7 days, within 30 days, and 30 – 180 days, respectively.[18] For specific pneumonia, this declining risk over time of pneumonia risk was also found for CAP.[17,42] A study revealed that the risk of pneumonia at 180 days or longer was found but not statistically significant.[21] The declining trend of pneumonia risk could be attributable to the adjustment of the body to compensate for the depleted acid secretion in the gastrointestinal and respiratory system. The adapted acid secretion known as hypersectrion of acid (or hypergastrinemia) could be done through three pathways. First, hypergastrinemia could be a result of the increased gastrin sectreion which is the reflex to the increased pH caused by lower gastric acid secretion through the PPI's inhibitory effect on H^+/K^+-ATPase enzyme.[43] Second, the adapted increase in number of parietal cells and enterochromaffin-like cells (ECL cells) as a response to a long-standing hypergastrinemia could cause more acid secretion.[44,45] Third, the upregulation of H^+/K^+-ATPase enzyme in the parietal cells as an adaptive response to a long suppressed acid secretion results in an increase in number of H^+/K^+-ATPase enzyme.[46] These adaptive mechanisms could be obvious after a continuous use of PPI of at least 8 weeks.[47]

In terms of cumulative dose of PPIs, the risk was found significant with the dose of less than 50 DDD and 50 – 100 DDD with crude ORs of 1.87 and 1.99, respectively, compared with no PPI use, but not with the dose of more than 100 DDD. This finding was consistent with a previous study where risk seemed to slightly drop when compared with the low and

medium cumulative dose of PPI with ORs of 1.4, 1.6 and 1.4 for less than 50 DDD, 50 – 100 DDD, and more than 100 DDD, respectively.[48] The meta-analysis study also indictaed that the risk increased once the dose increased from less than 50 DDD to 50 – 100 DDD, but the risk was lower than that of 50 – 100 DD when the dose increased further to more than 100 DDD.[18] The trend of declining risk of pneumonia at the higher cumulative dose was found in most studies including our present study.

The insignificant risk of pneumonia in pateints using more than 100 DDD in our study could be associated with the adaptive mechanisms described previously. For those taing single dose of PPIs, 100 DDD could be equal to 100 days or about 3 months of treatment. For those taking double dose, 100 DDD could mean 50 days or about 2 months of treatment. The duration of 2 to 3 months of PPI use is somewhat corresponding to the time window for adaptive mechanisms to compensate for the depleted acid secretion in the gastrointestinal and respiratory systems.[43-47] As a result, more acid is secreted and less risk of pneumonia was found among those with cumulative dose of more than 100 DDD to the level where no statistical significance was found. However, the interpretation of this result should be cautious since there was a relatively small number of participants taking more than 100 DDD.

Age was also significantly associated with pneumonia risk especially among those aged 60 years or older (adjusted OR =3.92), but not those 40 – 60 years old when compared with those aged younger than 40 years. This finding was consistent with a study where patients using PPIs for non-traumatic intracranial hemorrhage aged 65 years or older had a significantly higher risk of pneumonia (OR = 2.62, 95% CI = 1.49 - 4.59) compared with those aged less than 40 years. [25] They also found that patients aged 40 – 64 years did not have higher risk[25] similar to what we found in our study. Another study also reported a higher risk of pneumonia among patients older than 60 years with the use of PPIs (OR = 1.5, 95% CI = 1.3 - 1.7).[48] In addition, once the duration of PPI use was considered, those with 1 year of continuous PPI use had a highe risk of pneumonia (OR = 1.67, 95% CI = 1.37 – 2.02), and the risk further increased with 2 years of use (OR = 3.03, 95% CI = 2.60 – 3.53).[49] Physiological decline respective to increasing age could weaken physical and physiological functions of the lung including decreased elasticity, increased volume of trapped air, and decreased strength of the lung. These make the patients breathe more rapidly, hence the risk of inhaling bacteria into the lung. In addition, since immunity decreases with aging, the old patients could be infected more easily. Furthermore, the eldery patients are more likely to cough or aspirate which could allow for infection and hence the pneumonia.[50] On the other hand, in those younger patients, i.e., those aged 40 – 60 years of age, their lungs are still physiologically healthy and the risk of pneumonia could be less as insignificant risk was shown in our study.

Our study found that kidney failure was associated with an increased pneumonia risk associated with PPI use by 5.15 folds of those without the failure. This finding was consistent with the study from Taiwan where patients with chronic kidney disease had a 2.21-fold risk of pneumonia (95% CI = 1.59 – 3.07, *P*-value < 0.001) compared with those without the failure.[26] The risk of pneumonia among PPI use among patients with kidney failure increases by 10 – 20%. This increased risk was thought to be a unique abnormal responsive reaction of patienst using PPI to cause kidney inflammation known as aute interstitial nephritis (AIN) which is the humoral- and cell-mediated hypersensitivity reaction. This reaction causes the inflammation of the ureter and interstitium, followed by the acute kidney failure.[51] Since kidney failure could cause gastrointestinal disorders regarding the acid hypersecretion, PPIs were then prescribedfor such gastrointestinal illness. Hence the risk of pneumonia could be increased.[26]

Hematologicl disorders could also increase the risk of pneumonia using PPIs. Main disorders included anemia and thalassemia. These blood cell abnormalities could directly affect the immune system, especially thalassemia which could dramatically reduce the umber of neutrophil and the number and function of natural killer cells, increase the number and function of CD8 suppress cells, which could further enhance the risk of infection.[52] Patients with hematological disorders usually need iron supplement from medications and nutritional supplements. Unfortunately, iron could stimulate gastric acid secretion, which could increase the chance of PPI use, hence the increased risk of pneumonia.

Respiratory factors were found to associate with pneumonia risk among patients using PPI. These factors included smoking, respiratory disorders especially asthma and COPD, and medications for eye, ear, nose and throat illnesses of which many of them contained steroids and bronchodilators.

These three factors could increase the risk of pneumonia with direct suppression of the immunity of the respiratory system, especially on white blood cells, which lead to infection.[53,55,56] These three factors could also increase the chance of acid reflux from the stomach by increasing acid secretion, lowering the pressure of the lower esophageal sphincter (LES)[54,57], or increasing the pressure between thorax and abdomen, which could force the gastric acid to move to LES.[58] In some patients with poor control of respiratory illness, cough and heavy breathing could also promote acid reflux or aspiration.[48] With all factors mention in addition to promoting factors such as smoking with COPD, certain patients had upper gastrointestinal disorders especially GERD, hence a higher likelihood of using PPI. The finding in our study regarding respiratory disorders especially COPD was consistent with a previous study in Taiwan where COPD patienst using PPI had a higher risk of pneumonia (OR = 1.76, 95% CI = 1.33 - 2.34).[27]

The use of other medications could also affect the likelihood of having pneumonia among patients with PPI use. Analgesic/anti-inflammatory drugs were associated with a lower risk of pneumonia with an OR of 0.62 compared with those not taking these analgesic/anti-inflammatory drugs. These medications included mostly non-steroidal anti-inflammatory drugs (NSAIDs). The possible mechanism could be the anti-inflammation in the lung of these drugs. In addition, in actual practice, the elderly patients using long-term NSAIDs were prescribed PPI for prevention of NSAID-related gastrointestinal complications, especially those with history of upper gastrointestinal disorders.[59] The long-term use of PPI could in turn lead to the adaptive acid secretion and hence lead to a lower risk of pneumonia.[43-46] The use of analagesic/anti-inflammatory drugs could then indirectly improve the risk of pneumonia through the long-term use of PPI.

Factors that were not significantly associated with pneumonia included gender, age of 40 – 60 years old, autonomic nervous system drugs, antibiotic/cytotoxic drugs, vitamins, minerals, and supplements, and cancers. A study by Hermos and colleagues found no association between cancers and CAP among patients using PPI (adjusted OR = 0.93, 95% CI = 0.52 – 1.66).[33] Regarding gender, men usually had a lower risk of upper gastrointestinal disorders than women[39], hence a lower chance of PPI use and subsequent pneumonia. However, we found no difference in our study. This finding was consistent with the study in patients with non-traumatic intracranial hemorrhage who used PPIs[25] and a study of CAP in patients using esomeprazole.[60] However, one study found that women were significantly likely to have CAP compared with men (OR = 1.7, 95% CI = 1.5 - 2.0).[48]

This present study was the first investigation on the PPI use and risk of pneumonia among Thai patients. The study had certain limitations. With the unmatched case-control study design, certain unknown confounders could not be fully controlled for, especially age, or certain co-morbidities, to distribute evenly in the cases and controls. Even though statistical adjustment based potential confounders, the less bias from the sample selection step using matched case-control design could handle the bias better. Matching based on age and gastrointestinal disorders could have resulted in a less biased and more reliable finding. This study used retrospective data from hospital database. Therefore, some other information from interview could no be obtained, for example, compliance to medication use, which could affect the outcome of pneumonia. Our study had a relatively small sample size, therefore subgroup analysis on certain aspects could not be done with adequate statistical power. Based on our findings and study conduct, we proposed that studies with larger sample size, and with matching on potential confounders should be conducted. The better future research should be cohort study where more complete information on potential confounder could be obtained.

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